Int J Clin Exp Med 2020;13(11):8915-8923
www.ijcem.com /ISSN:1940-5901/IJCEM0119122

Original Article

Drug resistance of mycobacterium tuberculosis and its influencing factors

Wenyuan Zhu[1], Guiling Zhang[1], Lijun Zhu[2]

Departments of [1]Infectious Diseases, [2]Laboratory, The Affiliated Yangming Hospital of Ningbo University, Yuyao People's Hospital of Zhejiang Province, Yuyao, Zhejiang Province, China

Received July 28, 2020; Accepted September 2, 2020; Epub November 15, 2020; Published November 30, 2020

Abstract: Objective: Tuberculosis is currently a chronic infectious disease severely harming human health and the leading cause of single pathogen-induced death worldwide. This manuscript aims to investigate the drug resistance and its influencing factors of tuberculosis in different regions of China. Methods: A total of 1,831 patients in the Affiliated Yangming Hospital of Ningbo University, Yuyao People's Hospital of Zhejiang Province from January 2010 to December 2018 were involved in this study. These patients received initial treatment and retreatment of pulmonary tuberculosis that had positive acid-fast staining sputum smears. Results: Total drug resistance rate of mycobacterium tuberculosis was 30.48%. The total drug resistance rate in patients with initial treatment was 25.81%, which were significantly lower than that (41.90%) in patients with retreatment (both $P<0.05$); single-drug resistance rate, poly-drug resistance rate, multi-drug resistance rate and extensive drug resistance rate were 16.00%, 8.41%, 6.06% and 0.16%, respectively. The resistant drugs were S, H, R, E, Ofx and Km. Multivariate logistic regression analysis showed that Smoking, rural registered permanent residence, history of prior treatment, and history of treatment interruption were independent risk factors influencing drug resistance in patients with pulmonary tuberculosis with odds ratio values of 1.78 (95% confidence interval (CI: 1.17-2.28), 1.96 (95% CI: 1.41-2.47), 2.34 (95% CI: 1.85-2.78) and 1.86 (95% CI: 1.34-2.32), respectively. The increased risk of multi-drug resistance was significantly correlated with previous treatment history and interruption of treatment, and the OR was 2.18 (95% CI: 1.76-2.59) and 2.35 (95% CI: 1.86-2.87), respectively (both $P<0.05$). Conclusion: The drug resistance situation in tuberculosis in the Affiliated Yangming Hospital of Ningbo University, Yuyao People's Hospital of Zhejiang Province was severe. Smoking, rural registered permanent residence, history of prior treatment, and history of treatment interruption were independent risk factors influencing drug resistance in patients with pulmonary tuberculosis. History of prior treatment and history of treatment interruption were independent risk factors of multi-drug resistant tuberculosis.

Keywords: Pulmonary tuberculosis, mycobacterium, drug resistance, risk factor

Introduction

Tuberculosis is currently a chronic infectious disease severely harming human health and the leading cause of single pathogen-induced death worldwide [1]. In 2015, the morbidity and mortality rates of tuberculosis in China accounted for 15.32% and 3.90% of the world, respectively, and China has become one of the countries with the most severe burden of tuberculosis in the whole world [2]. Therefore, tuberculosis has been one of the severe diseases that was emphatically controlled in China. Since 2001, Chinese government has successively set the National Tuberculosis Control Program 2001-2010 and National Tuberculosis Control Program 2011-2015 to fully implement modern tuberculosis control strategy. In China, tuberculosis has been effectively controlled, and both mycobacterium tuberculosis infection rate and the morbidity rate of smear-positive tuberculosis are decreasing year by year [3]. However, the morbidity rate of drug-resistant tuberculosis is increasing in recent years. A systematic analysis showed that the drug resistance rates in patients with initial treatment and retreatment of tuberculosis were 20.1% and 49.8% respectively, and the multi-drug resistance rates were 4.8% and 26.3% respectively [4]. Drug resistance, especially for multi-drug resistance of tuberculosis, has become an important issue to be solved urgently for the

prevention and control of tuberculosis in China [5].

Drug resistance in tuberculosis differs in different regions of China. In a study on the drug resistance of mycobacterium tuberculosis in 6 provinces in China, the drug resistance rate in tuberculosis is the highest in Henan Province (42.98%), and the lowest is in Beijing (21.50%) [6]. In addition, previous studies reported that age, gender, smoking, place of residence, intrapulmonary cavity, history of prior treatment and other factors might be related to the increase of drug resistance in tuberculosis, although these results were not necessarily consistent [7-10]. This study aimed to analyze the drug resistance in tuberculosis and related risk factors in Zhejiang Province, with the hope to provide scientific evidence for the prevention and control of tuberculosis in this area.

Materials and methods

Patients

Patients with initial treatment and retreatment of pulmonary tuberculosis who had positive acid-fast staining sputum smears detected in tuberculosis drug resistance surveillance sites of The Affiliated Yangming Hospital of Ningbo University, Yuyao People's Hospital of Zhejiang Province from January 2010 to December 2018 were involved in this study. The tuberculosis drug resistance surveillance sites located in ten cites.

Patients with initial treatment were defined as the patients never treated with anti-tuberculosis drugs or treated with anti-tuberculosis drugs for less than 1 month; while those treated over 1 month were re-treated patients [8]. Individual information and tuberculosis diagnosis and treatment information of patients were gathered using questionnaires. Investigators were composed of specialized persons or related medical personnel from tuberculosis dispensaries. All participants signed the informed consent and this study has been approved by the Ethics Committee of Yuyao People's Hospital of Zhejiang Province.

Sputum culture and drug sensitivity test

Sputum specimens were collected by each surveillance site, and strain identification was performed using PNB/TCH differential medium [6]. Drug sensitivity of mycobacterium tuberculosis from patients with positive sputum culture was tested in a provincial laboratory by the proportion method with starch-free modified Loewenstein-Jenson medium as the control and basal medium [11]. The tested drugs included four first-line anti-tuberculosis drugs isoniazide (H), rifampicin (R), ethambutol (E), streptomycin (S), as well as two second-line drugs levofloxacin (Ofx) and kanamycin (Km). Drug resistance was judged according to drug resistance percentage. Drug resistance percentage (%) = number of bacterial colonies grown on medicated medium/number of bacterial colonies grown on the control medium * 100. If the drug resistance percentage ≥1%, the tested mycobacterium tuberculosis strain was considered drug resistant, otherwise the strain was considered as drug sensitive.

Definition of drug resistance

Total drug resistance: drug resistance to any one or more of 6 anti-tuberculosis drugs. Single-drug resistance: Drug resistance to one anti-tuberculosis drug. Poly-drug resistance: Drug resistance to more than one anti-tuberculosis drug (excluding drug resistance to H and R simultaneously). Multi-drug resistance: Drug resistance to H and R simultaneously at least. Extensive drug resistance: Besides drug resistance to H and R simultaneously, drug resistance to one or more of fluoroquinolone antibiotics (including Ofx) and three second-line anti-tuberculosis drugs (capreomycin, kanamycin and amikacin) [12].

Quality control

Sputum smears and laboratory consumable during mycobacterium tuberculosis culture were provided by Tuberculosis Reference Laboratory of Zhejiang Province. In drug sensitivity test, standard strain HRv37, sensitive strain and drug resistance strain of mycobacterium tuberculosis were used as the control of quality. In addition, the Provincial Tuberculosis Reference Laboratory regularly checked up and tested each Municipal Reference Laboratory. Checking contents included blinded-rechecking sputum smears, and evaluation indexes were the positive rate, negative rate and total coincidence rate of smears, so as to ensure

Table 1. Total drug resistance in patients with initial treatment and retreatment (n, %)

Patients	Drug Resistance	Initial Treatment (n=1,302)	Retreatment (n=529)	χ^2	P
Total Drug Resistance	558 (30.48)	336 (25.81)	222 (41.97)	46.36	<0.001
Single-drug Resistance	293 (16.00)	194 (14.90)	99 (18.71)	4.07	0.044
Poly-drug Resistance	154 (8.41)	93 (7.14)	61 (11.53)	9.40	0.002
First-line Drug	109 (5.95)	70 (5.38)	39 (7.37)	2.68	0.102
Containing Second-line Drug	45 (2.46)	23 (1.77)	22 (4.16)	8.98	0.003
Multi-drug Resistance	111 (6.06)	49 (3.76)	62 (11.72)	41.82	<0.001
Extensive Drug Resistance	3 (0.16)	0 (0.00)	3 (0.57)		0.024

accuracy and scientific running of laboratory operations.

Outcome measurements

Outcome measurements: Various drug resistance rates calculated according to the above definition of drug resistance; risk factors influencing drug resistance and multi drug resistance in tuberculosis.

Statistical analysis

SPSS 20.0 software was used to analyze the data. The drug resistance rate was expressed in constituent ratio. Comparison in drug resistance rate between patients with initial treatment and retreatment was performed using chi-square test or exact probability. According to the drug resistance situation in drug sensitivity test, patients with pulmonary tuberculosis were divided into case group and control group. Differences in individuals or clinical features between case group and control group were compared using chi-square test to perform univariate analysis, and variables with significant difference in univariate analysis were brought into multivariate logistic regression analysis to analyze risk factors influencing drug resistance and multi-drug resistance in patients with tuberculosis. In multivariate logistic regression analysis, likelihood ratio test was carried out based on maximum local likelihood, and forward stepwise independent variable selection was performed; norms of including and excluding model were defined as 0.05 and 0.10 respectively. Analogously, sensitive patients and multi-drug resistant patients in drug sensitivity test were set as case group and control group, and risk factors influencing multi-drug resistance were analyzed using the above univariate analysis and logistic regression model. The level of statistical significance was set at bilateral α=0.05.

Results

General information

A total of 1,840 patients with tuberculosis were recruited during January 2010 and December 2018, and of them 9 patients who were with non-mycobacterium tuberculosis by strain culture identification were excluded. Thus, a total of 1,831 patients were involved in this study, including 1,302 patients with initial treatment (71.11%) and 529 re-treated patients (28.89%). Of the isolated strains from 1,831 patients, 558 strains showed drug resistance to any one of 6 anti-tuberculosis drugs, with a total drug resistance rate of 30.48%. The total drug resistance rate in patients with initial treatment was 25.81% which was significantly lower than that in re-treated patients (41.97%). The single-drug resistance rate, poly-drug resistance rate, multi-drug resistance rate and extensive drug resistance rate in patients were 16.00%, 8.41%, 6.06% and 0.16%, respectively, and these four drug resistance rates in patients with initial treatment were significantly less than those in re-treated patients (all P<0.05, **Table 1**).

The drug resistant spectrum of strains from 1,831 patients with pulmonary tuberculosis was shown in **Table 2**. There were 6 poly-drug resistance combinations of 4 first-line anti-tuberculosis drugs, and the proportion of H+S among patients with initial treatment was the largest, accounting for 80.00%. In the poly-drug resistance combinations of supplementation with second-line drugs, the proportions of S+Ofx and H+S+Ofx were the top two, accounting for 21.74% and 13.04%, respectively.

Table 2. Drug resistant spectrum of mycobacterium tuberculosis in patients with smear-positive pulmonary tuberculosis

Anti-tuberculosis drug	Initial treatment		Retreatment		Total	
	Number	Percentage (%)	Number	Percentage (%)	Number	Percentage (%)
Single-drug Resistance						
H	35	18.04	26	26.26	61	20.82
R	14	7.22	8	8.08	22	7.51
E	10	5.15	7	7.07	17	5.80
S	127	65.46	55	55.56	182	62.12
Ofx	6	3.09	2	2.02	8	2.73
Km	2	1.03	1	1.01	3	1.02
Subtotal	194	100.00	99	100.00	293	100.00
Multi-drug Resistance						
H+S	56	80.00	14	35.90	70	64.22
H+E	2	2.86	8	20.51	10	9.17
H+S+E	3	4.29	7	17.95	10	9.17
R+E	1	1.43	2	5.13	3	2.75
R+S	6	8.57	6	15.38	12	11.01
R+E+S	2	2.86	2	5.13	4	3.67
Subtotal	70	100	39	100.00	109	100.00
Poly-drug Resistance Containing Second-line Drug						
H+Ofx	3	13.04	0	0.00	3	6.67
H+S+Ofx	4	17.39	0	0.00	4	8.89
H+S+Km	0	0.00	1	4.55	1	2.22
H+S+Km+Ofx	0	0.00	2	9.09	2	4.44
H+E+S+Km	2	8.70	1	4.55	3	6.67
H+E+Ofx	0	0.00	3	13.64	3	6.67
H+E+S+Km+Ofx	0	0.00	4	18.18	4	8.89
R+Ofx	2	8.70	2	9.09	4	8.89
R+E+Ofx	3	13.04	2	9.09	5	11.11
R+E+S+Km	3	13.04	1	4.55	4	8.89
E+S+Ofx	1	4.35	1	4.55	2	4.44
E+S+Km	0	0.00	2	9.09	2	4.44
S+Km	0	0.00	2	9.09	2	4.44
S+Ofx	5	21.74	1	4.55	6	13.33
Subtotal	23	100.00	22	100.00	45	100.00
Multi-drug Resistance						
H+R	12	24.49	1	1.61	13	11.71
H+R+E	6	12.24	3	4.84	9	8.11
H+R+S	8	16.33	21	33.87	29	26.13
H+R+Ofx	2	4.08	5	8.06	7	6.31
H+R+E+S	16	32.65	5	8.06	21	18.92
H+R+S+Ofx	0	0.00	9	14.52	9	8.11
H+R+S+Km	2	4.08	1	1.61	3	2.70
H+R+E+S+Ofx	3	6.12	13	20.97	16	14.41
H+R+E+S+Km	0	0.00	1	1.61	1	0.90
H+R+S+Ofx+Km	0	0.00	1	1.61	1	0.90
H+R+E+S+Ofx+Km	0	0.00	2	3.23	2	1.80
Subtotal	49	100.00	62	100.00	111	100.00

Note: H: isoniazide; R: rifampicin; E: ethambutol; S: streptomycin; Ofx: levofloxacin; Km: kanamycin.

There were 11 multi-drug resistance combinations, and the proportions of H+R+E+S, H+R and H+R+S were the top three, accounting for 32.65%, 24.49% and 16.33%, respectively. The

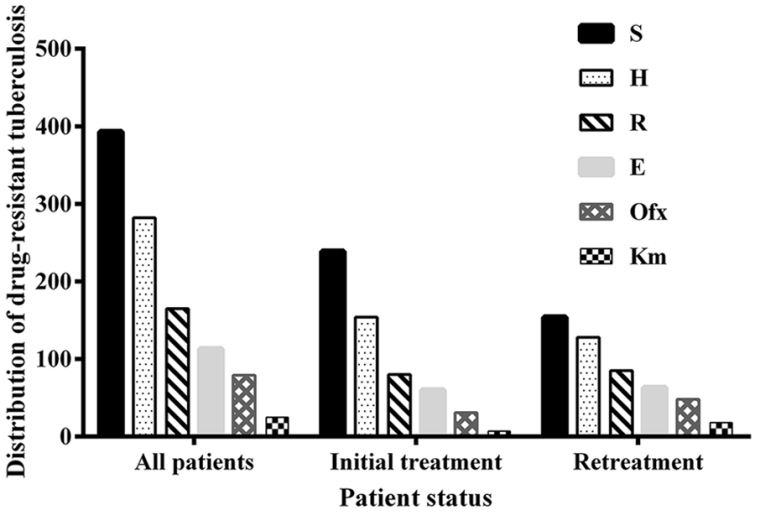

Figure 1. Sequence of drug resistance to 6 anti-tuberculosis drugs. S: streptomycin; H: The tested drugs included isoniazide; R: rifampicin; E: ethambutol; Ofx: levofloxacin; Km: kanamycin.

drug resistance rates from high to low were streptomycin (393 strains), isoniazide (282 strains), rifampicin (165 strains), ethambutol (113 strains), levofloxacin (75 strains) and kanamycin (25 strains), and the sequence of drug resistance to the 6 drugs in patients with initial treatment and retreatment was consistent with the above sequence (**Figure 1**).

Risk factors influencing drug resistance and multi-drug resistance in patients with pulmonary tuberculosis

Risk factors influencing drug resistance and multi-drug resistance were analyzed by taking patients who were sensitive to all 6 anti-tuberculosis drugs as control. Comparison in personal features and treatment between drug resistant and multi-drug resistant patients and control patients were shown in **Table 3**. Drug resistant patients over 60 years old, smoking, monthly family income less than 6,000 RMB, and rural registered permanent residence accounted for 26.88%, 49.46%, 64.70% and 55.20% respectively, which were significantly higher than those in control group (all P<0.05). In addition, the proportions of history of prior treatment and history of treatment interruption in drug resistance group were significantly higher than those in control group. In multi-drug resistance group, drug resistant patients over 60 years old, smoking, rural registered permanent residence, history of prior treatment and history of treatment interruption accounted for 33.33%, 53.15%, 49.55%, 37.84% and 22.52%, respectively, which were significantly higher than those in control group (all P<0.05).

The above results indicated that age, smoking, registered permanent residence, history of prior treatment and history of treatment interruption might be risk factors influencing drug resistance and multi-drug resistance. Moreover, low family income might also be a risk factor influencing drug resistance and multi-drug resistance. The results of multivariate logistic regression analysis indicated that smoking (odds ratio (OR)=1.78, 95% confidence interval (CI): 1.17-2.28), rural registered permanent residence (OR=1.96, 95% CI: 1.41-2.47), history of prior treatment (OR=2.34, 95% CI: 1.85-2.78) and history of treatment interruption (OR=1.86, 95% CI: 1.34-2.32) were independent risk factors influencing drug resistance in patients with pulmonary tuberculosis. The increasing risk of multi-drug resistance was significantly correlated with the history of prior treatment (OR=2.18, 95% CI: 1.76-2.59) and history of treatment interruption (OR=2.35, 95% CI: 1.86-2.87) (**Table 4**).

Discussion

The morbidity rate of tuberculosis has declined in China recently, while the morbidity rate of drug-resistant tuberculosis is increasing. The world health organization (WHO) has reported that patients with multi-drug resistant tuberculosis in China in 2018 accounts for 13% of the world, ranking second in the world [13]. Drug-resistant tuberculosis can lead to an increase in the difficulty of treatment and an enlargement in the range of chronic source of infection, greatly challenging the prevention and cure of tuberculosis in China.

We performed five nationwide epidemiological surveys of tuberculosis. In the latest survey (in 2010), the total drug resistance rate, multi-drug resistance rate and extensive drug resis-

Table 3. Univariate analysis of risk factors influencing drug resistance and multi-drug resistance of mycobacterium tuberculosis in patients with smear-positive pulmonary tuberculosis (n, %)

Feature	Sensitivity	Drug Resistance	P	Sensitivity	Multi-drug Resistance	P
Gender			0.141			0.478
Male	912 (71.64)	416 (74.55)		912 (71.64)	76 (68.47)	
Female	361 (28.36)	142 (25.45)		361 (28.36)	35 (31.53)	
Age			0.033			0.048
<30	252 (19.79)	85 (15.23)		252 (19.80)	19 (17.12)	
30-60	729 (57.27)	323 (57.89)		729 (57.27)	55 (49.55)	
>60	292 (22.94)	150 (26.88)		292 (22.94)	37 (33.33)	
Educational background			0.044			0.145
Senior high school and below	845 (66.38)	397 (71.15)		845 (66.38)	81 (72.97)	
Junior college and above	428 (33.62)	161 (28.85)		428 (33.62)	30 (27.03)	
Smoking			0.016			0.046
No	721 (56.64)	282 (50.54)		721 (56.64)	52 (46.85)	
Yes	552 (43.36)	276 (49.46)		552 (43.36)	59 (53.15)	
Monthly family income			0.027			0.036
<6000	754 (59.23)	361 (64.70)		754 (59.23)	77 (69.37)	
≥6000	519 (40.77)	197 (35.30)		519 (40.77)	34 (30.63)	
Registered permanent residence			<0.001			0.012
Rural area	487 (38.26)	308 (55.20)		487 (38.26)	55 (49.55)	
City	786 (61.74)	250 (44.80)		786 (61.74)	56 (50.45)	
History of prior treatment			<0.001			0.002
No	966 (75.88)	256 (45.88)		966 (75.88)	71 (63.96)	
Yes	307 (24.12)	302 (54.12)		307 (24.12)	42 (37.84)	
History of treatment interruption			<0.001			0.005
No	1107 (86.96)	442 (79.21)		1107 (86.96)	86 (77.48)	
Yes	166 (13.04)	116 (20.79)		166 (13.04)	25 (22.52)	

tance rate in patients with tuberculosis were 42.1%, 6.8% and 2.1%, and the drug resistance rates in patients with initial treatment and retreatment were 42.7% and 38.5% respectively [14]. In addition, due to the differences in geographic location, demographic characteristics, climate and other factors, the morbidity rate of drug-resistant tuberculosis in China shows significant regional differences [15-17]. In this study, the total drug resistance rate in 1,831 patients with tuberculosis was 30.48%; the total drug resistance rate and multi-drug resistance rate in patients with initial treatment were 25.81% and 6.06%, which were lower than the national level in 2010; the total drug resistance rate in re-treated patients was 41.97% which was slightly higher than the national level; the results was similar to those in another study [12, 14]. In general, the total drug resistance rate and multi-drug resistance rate in tuberculosis in this region were in the middle level in China [6, 12, 18]. In this study, the extensive drug resistance rate was 0.16% which was lower than that reported in the national survey of tuberculosis epidemiology in 2010 (2.1%) and lower than that reported in this region and other areas [14, 19].

In this study, the sequence of single-drug resistance rate was S, H, R, E, Ofx and Km, and the sequence of drug resistance to the 6 drugs in patients with initial treatment and retreatment was consistent with the above sequence. The results were consistent with those reported in previous studies [12, 20]. In another study, the drug resistance rates from high to low were S, H, R, O, E and Km [21]. However, the drug resistance rates to S, H and R were the top three, which was consistent with trend comparison. Due to the differences in geographical environment, climatic conditions, social customs and habits and economic level between different

Table 4. Multivariate logistic regression analysis of risk factors influencing drug resistance and multi-drug resistance of mycobacterium tuberculosis in patients with smear-positive pulmonary tuberculosis (n, %)

Feature	Adjusting OR	95% CI	P
Drug resistance*			
Smoking			
No	Reference		0.043
Yes	1.78	1.17-2.28	
Registered permanent residence			
Rural area	Reference		0.026
City	1.96	1.41-2.47	
History of prior treatment			
No	Reference		0.011
Yes	2.34	1.85-2.78	
History of treatment interruption			
No	Reference		0.031
Yes	1.86	1.34-2.32	
Multi-drug resistance#			
History of prior treatment			
No	Reference		
Yes	2.18	1.76-2.59	0.019
History of treatment interruption			
No	Reference		
Yes	2.35	1.86-2.87	0.007

Note: *Adjusting age, educational background, and monthly family income; #adjusting age, smoking, monthly family income, and registered permanent residence. OR: odds ratio; CI: confidence interval.

regions, the drug resistance rate and drug resistance sequence in The Affiliated Yangming Hospital of Ningbo University, Yuyao People's Hospital of Zhejiang Province were not consistent with those in other areas [6, 8, 14, 22]. Therefore, we should develop appropriate therapeutic regimens based on the results of mycobacterium tuberculosis culturing and drug sensitivity test in the prevention and cure of tuberculosis.

In this study, smoking, rural registered permanent residence, history of prior treatment and history of treatment interruption were independent risk factors influencing drug resistance in patients with tuberculosis, and multi-drug resistance was significantly correlated with history of prior treatment and history of treatment interruption, which was similar to but not fully consistent with the results in other studies [8, 23-25]. In a meta-analysis involving in 33 studies, smoking is an independent risk factor influencing drug resistance and multi-drug resistance. In other meta-analysis, smoking can increase the risk of multi-drug resistant tuberculosis but with no significant difference [23, 24]. Analogously, the significant correlation between smoking and drug resistance in this study was only existed in drug resistance not in multi-drug resistance. This might be related to the easy treatment interruption in smoking patients [26]. Previous studies reported that rural population or floating population might increase the risk of drug resistant tuberculosis [25, 27]. The result that rural registered permanent residence was an independent risk factor influencing drug resistance in tuberculosis in this study was consistent with that in above studies. The reason might be that tuberculosis control force in rural areas was relatively weak, and floating populations mostly came from rural areas and had worse living environment and few opportunities receiving medical services than permanent residents, making the drug resistant tuberculosis be prone to occur.

Previous studies have confirmed that history of prior treatment and treatment interruption are risk factors influencing drug resistance and multi-drug resistance in tuberculosis [8, 24, 28]. In this study, we also obtained the result, especially among risk factors influencing multi-drug resistance, only history of prior treatment and treatment interruption showed a significant difference, which emphasizing the significance of standard treatment in preventing drug resistance in the prevention and control of tuberculosis. Moreover, some studies indicated that female, age, educational background, financial situation and other factors were related to the increasing risk of drug resistant tuberculosis, which was not fully consistent with the results in our study [7, 28, 29]. Therefore, we should further investigate the correlations between the above factors and drug resistance and multi-drug resistance in tuberculosis.

In summary, we analyzed the epidemiological distribution of drug resistant tuberculosis and risk factors influencing drug resistance and multi-drug resistance in tuberculosis. The drug resistance in tuberculosis in The Affiliated Yangming Hospital of Ningbo University, Yuyao People's Hospital of Zhejiang Province is still severe. In future, we should improve the normalization of tuberculosis treatment, detect the drug resistance of mycobacterium tuberculosis timely, identify high-risk groups in accordance with risk factors influencing drug resistance and multi-drug resistance in tuberculosis in this region, and perfect tuberculosis prevention and control measures in this region.

Disclosure of conflict of interest

None.

Address correspondence to: Lijun Zhu, Department of Laboratory, The Affiliated Yangming Hospital of Ningbo University, Yuyao People's Hospital of Zhejiang Province, No. 800 Chengdong Road, Yuyao 315400, Zhejiang Province, China. Tel: +86-0574-62619229; E-mail: zhulijunyy80@163.com

References

[1] GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017; 390: 1151-1210.

[2] Zhu S, Xia L, Yu SC, Chen SB and Zhang JY. The burden and challenges of tuberculosis in China: findings from the Global Burden of Disease Study 2015. Sci Rep 2017; 7: 14601.

[3] Guo ZY, Xiao D, Wang XH, Wang YY and Yan TC. Epidemiological characteristics of pulmonary tuberculosis in mainland China from 2004 to 2015: a model-based analysis. BMC Public Health 2019; 19: 219.

[4] Duan QH, Chen Z, Chen C, Zhang ZB, Lu ZQ, Yang YL and Zhang L. The prevalence of drug-resistant tuberculosis in mainland China: an updated systematic review and meta-analysis. PLoS One 2016; 11: e0148041.

[5] Long Q, Qu Y and Lucas H. Drug-resistant tuberculosis control in China: progress and challenges. Infect Dis Poverty 2016; 5: 9.

[6] Song Y, Wan L, Chen SS, Xu YJ, Liu ZG, Zhao XQ, Liu HC, Wu YM, Wan KL, Guan CX and Liu M. Analysis on drug resistance of Mycobacterium tuberculosis and influencing factors in six provinces of China. Chin J Epidemiol 2016; 37: 945-948.

[7] Liu Q, Zhu LM, Shao Y, Song HH, Li GL, Zhou Y, Shi JY, Zhong CQ, Chen C and Lu W. Rates and risk factors for drug resistance tuberculosis in Northeastern China. BMC Public Health 2013; 13: 1171.

[8] Lv XT, Lu XW, Shi XY and Zhou L. Prevalence and risk factors of multi-drug resistant tuberculosis in Dalian, China. J Int Med Res 2017; 45: 1779-1786.

[9] Wan DY, Hu YF and C TG. Analysis of clinical factors affecting drug resistance of mycobacterium tuberculosis. Lab Med Clin 2017; 14: 3309-3310+3312.

[10] Cai XL, Zhang DD, Yan YQ, Tan DX and Xu YH. Meta-analysis on risk factors of multidrug resistant tuberculosis in China. Chin J Epidemiol 2015; 36: 1424-1429.

[11] NBSP, WHO, Programme GT, Tuberculosis IUA and Disease L. Guidelines for surveillance of drug resistance in tuberculosis 1997. Geneva Switzerland Who Glob Tuberc Programme 1997; 2: 71-89.

[12] Zhang TH, Liu WP, Li Y, Deng YL, Sun XL, Liu CL and Liu Y. Analysis of drug resistance surveillance of tuberculosis in Shaanxi. Chin Trop Med 2017; 17: 226-230.

[13] World Health Organization. Global tuberculosis report Geneva 2018. Switzerland: World Health Organ 2018.

[14] Wang LX, Cheng SM, Chen MT, Zhao YL, Zhang H, Jiang SW, He GX, Lv Q, Du X, Chen W, Liu XQ, Ruan YZ, Wang SF, Xia YY, Yu L, Li J and Li X. The fifth national tuberculosis epidemiological survery in 2010. Zhongguo Fanglao Zazhi 2012; 34: 485-508.

[15] He GX, Zhao YL, Jiang GL, Liu YH, Xia H, Wang SF, Wang LX, Borgdorff MW, van der Werf MJ and van den Hof S. Prevalence of tuberculosis drug resistance in 10 provinces of China. BMC Infect Dis 2008; 8: 166.

[16] Zhou M, Liu S, Li QF, Wang QM, Zhu M, Cao L, Wang DM, Xu YH, Zheng TL, Ye Q, Hu XY, Zuo HJ and Pei XF. Drug resistance characteristics of Mycobacterium tuberculosis isolates between 2014 and 2017 in Sichuan, China: a retrospective study. PLoS One 2018; 13: e0209902.

[17] Li QC, Zhao G, Wu LM, Lu M, Liu W, Wu YF, Wang L, Wang K, Qian HZ and Xie L. Prevalence and patterns of drug resistance among pulmonary tuberculosis patients in Hangzhou, China. Antimicrob Resist Infect Control 2018; 7: 61.

[18] Chen C, Li RZ, Chen MT, Zhao YL and Wang LX. Drug resistant tuberculosis in China-an analysis on results of national tuberculosis epidemiological sampling surveys and drug resis-

tance surveillance. Dis Surveill 2013; 28: 265-268.
[19] Liao S, Cai C, Huo FM, Wu JN, Kong CC, Huang HR, Xu SF and Sun ZG. Trends in drug-resistant tuberculosis in China: data from a clinical tuberculosis centre. Int J Tuberc Lung Dis 2017; 21: 990-995.
[20] Zhao LF and Liu YM. Analysis on drug resistance of Mycobacterium tuberculosisin Xi'an Chest Hospital from 2013 to 2015. Drugs Clin 2015; 30: 1542-1545.
[21] Li Y, Wang XD, Chen ML, Yang J, Wang R, Xian XP and Zhang TH. Analysis of drug resistance of Mycobacterium tuberculosis during past 6 years in Shaanxi area. J Clin Pulm Med 2017; 22: 1489-1492+1526.
[22] Chen SH, Wu BB, Liu ZW, He HB, Pan AZ, Wang F, Zhang MW, Zhou L, Zhang Y and Wang XM. An analysis on the epidemic characteristics of tuberculosis drug resistance in Zhejiang Province. J Prev Med 2016; 28: 757-761+765.
[23] Wang MG, Huang WW, Wang Y, Zhang YX, Zhang MM, Wu SQ, Sandford AJ and He JQ. Association between tobacco smoking and drug-resistant tuberculosis. Infect Drug Resist 2018; 11: 873-887.
[24] Feng M, Xu YG, Zhang XY, Qiu Q, Lei SG, Li JL, Yuan W, Song QF and Xu JH. Risk factors of multidrug-resistant tuberculosis in China: a meta-analysis. Public Health Nurs 2019; 36: 257-269.
[25] Yu SF, Mei XD, Kan XH, Fang XH and Bao XD. Risk factors of multidrug-resistant tuberculosis in Anhui Province: a case-control study. Chin J Dis Control Prev 2016; 20: 1026-1028.
[26] Gennaro FD, Pizzol D, Cebola B, Stubbs B, Monno L, Saracino A, Luchini C, Solmi M, Segafredo G, Putoto G and Veronese N. Social determinants of therapy failure and multi drug resistance among people with tuberculosis: a review. Tuberculosis (Edinb) 2017; 103: 44-51.
[27] Wang JJ, Zhou ML, Du YX, Chen C, Chen Z, Chen J, Zheng CL and Wang WH. Analysis on the influential factors of drug resistance and multidrug resistant tuberculosis in Wuhan city. Chin J Dis Control Prev 2017; 21: 164-167.
[28] Hameed S, Ahmad SR, Rahman MAU, Nazir H and Ullah I. Drug resistance profile of Mycobacterium tuberculosis and predictors associated with the development of drug resistance. J Glob Antimicrob Resist 2019; 18: 155-159.
[29] Wang SF, Zhou Y, Pang Y, Zheng HW and Zhao YL. Prevalence and risk factors of primary drug-resistant tuberculosis in China. Biomed Environ Sci 2016; 29: 91-98.